DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 1/19/10 is acknowledged. Claims 4-6, 9-14, 18-65, 69-77 and 79-80 are cancelled. Claim 3 is currently amended. Claims 1-3, 7, 8, 15-17, 66-68 and 78 are pending in this application.

2. On p. 4 of the response, Applicant requested to clarify the status of claim 68. In response, due to the examiner's typographical error, claim 68 was erroneously excluded in the previous office action. Claim 68 is now included and examined in this office action.

3. Claims 1-3, 7, 8, 15-17, 66-68 and 78 are under examination with respect to an ***in vitro*** method of making a transplant cell population and promoting its viability by ***in vitro*** treatment of cells with ursodeoxycholic acid (UDCA) or its analog in this office.

4. Applicant's arguments filed on 1/19/10 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

5. The rejection of claims 1-3, 7, 8, 15-17, 66-68 and 78 rejected under 35 U.S.C. 103(a) as being unpatentable over Duan et al. (Cell Transplantation. 2002, vol. 11, pages 195-205) in view of Falasca et al. (Transplantation. May 2001, Vol. 71, No. 9, pages 1268-1276, as in IDS) Rodrigues et al. (Journal of Neurochemistry. 2000, Vol. 75, pages 2368-2379, as in IDS), and Silva et al. (Journal of Hepatology. 2001, Vol. 34,

pages 402-408) is withdrawn in response to Applicant's arguments on p. 5-6 of the response and Applicant's declaration under 37 CFR 1.132.

The declaration under 37 CFR 1.132 filed 1/19/10 is sufficient to overcome the rejection of claims 1-3, 7, 8, 15-17, 66-68 and 78 rejected under 35 U.S.C. 103(a) based upon the references of Duan et al. (Cell Transplantation. 2002, vol. 11, pages 195-205) in view of Falasca et al. (Transplantation. May 2001, Vol. 71, No. 9, pages 1268-1276, as in IDS) Rodrigues et al. (Journal of Neurochemistry. 2000, Vol. 75, pages 2368-2379, as in IDS), and Silva et al. (Journal of Hepatology. 2001, Vol. 34, pages 402-408).

Claim Rejections/Objections Maintained

In view of the amendment filed on 1/19/10, the following rejections are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

On p. 4-5 of the response, Applicant argues that the scope of claim 3 is clear because claim 3 does not improperly recite both narrow and broad ranges. In addition, Applicant argues that claim 3 has been amended to recite "the method of claim 1 wherein the precursors thereof are selected from...." to clarify the invention. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's arguments, amended claim 3 still recites both narrow and broad limitations. Note that independent claim 1 recites "human dopamine neurons or precursor thereof", which is a narrower limitation. The limitation of "human dopamine neurons or precursor thereof" is the cell lineages that have already committed to dopaminergic neurons, dopaminergic progenitor or precursor cells. However, the limitation "the group consisting of pluripotent stem cells, embryonic stem cells, adult stem cells and combinations thereof" in dependent claim 3 is a broader limitation. The recitations " pluripotent stem cells, embryonic stem cells, adult stem cells" are the stem cells that have not committed to or developed into the cell lineages of dopaminergic neurons, progenitor or precursors. These recited stem cells are multipotent and can develop into different cell types and different neuronal populations, progenitor or precursor cells other than dopaminergic neurons/progenitors/precursors. Thus, claim 3 recites both narrow and broad limitations because claim 1 has a narrower limitation, which renders claim 3 indefinite. Accordingly, the rejection of claim 3 rejected under 35 U.S.C. 112, second paragraph, as being indefinite is maintained.

New Grounds of Rejection

The following rejections are new grounds of rejections necessitated by the amendment and declaration filed 1/19/10.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7, 8, 15-17, 66-68 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keene et al. (Exp. Neurol. 2001. 171: 351-360 as in IDS) as evidenced by Prochiantz et al. (Proc. Natl. Acad. Sci. USA, 1979. 76: 5387-5391) in view of US Patent No. 6497872 (Weiss et al., issued on Dec 24, 2002, filed June 7, 1995).

Claims 1-3, 7, 8, 15-17, 66-68 and 78 as amended, are directed to a method of promoting viability of a transplant cell population comprising contacting the transplant cell population *in vitro* with an effective amount of a compound selected from the group consisting of ursodeoxycholic acid (UDCA), a salt thereof, an analog thereof and a combination thereof, wherein the cells of the prepared transplant cell population are human dopamine neurons or precursors thereof. Dependent claims are directed cells from autologous, heterologous or xenologous tissues (claims 16-17), pluripotent, embryonic, adult stem cells (claims 3 and 78), and human embryonic ventral mesencephalic cells (claim 68). Dependent claims are further directed to contacting the cells with UDCA or its analog in combination with pharmaceutically acceptable carrier (claim 15), UDCA analog such as tauroursodeoxycholic acid (TUDCA) (claims 66-67).

Keene et al. teach a method of promoting viability of a transplant cell population comprising contacting the transplanted cell population in vitro an effective amount of a compound selected from the group consisting of ursodeoxycholic acid, a salt, an analog and a combination thereof wherein the transplant cell population are cultured embryonic rat striatal cells (which include dopamine neurons or precursor thereof and embryonic stem cells) as recited in instant claims 1-3, 7,15, 66-67 and 78 (see p. 352, 4^{th}-5^{th} paragraphs, in particular). Keene teaches that a method of reducing striatal degeneration in the 3-nitropropionic acid (3-NP) model of Hungtington disease by Tauroursodeoxycholic acid (TUDCA) (see p. 351-353, in particular). Keene teaches that TUDCA prevents 3-NP-induced neuronal cell death in cultured E18 embryonic striatal cells and in vivo as in claims 1-3, 7,15, 66-67 and 78 (see p. 352, col.1-2; p. 354-356,

in particular). It is noted that cultured embryonic striatal cells disclosed by Keene et al encompass dopamine neurons as evidenced by Prochiantz et al. (see p. 5387, abstract; p. 5387-5388, materials and methods, Proc. Natl. Acad. Sci. USA, 1979, 76:5387-5391). In addition, although Keene does not explicitly teach pluripotent, embryonic stem cells or adult stem cells as in claims 3 and 78, it is noted that the cells in the striatal cell culture disclosed by Keene are from E18 embryonic striatum brain areas, which encompass pluripotent stem and embryonic stem cells as in claim 3, and are embryonic ventral mesencephalic cells as in claim 78. In addition, the TUDCA is in a culture medium or in saline, which meets the limitation of "the compound in combination with a pharmaceutical acceptable carrier" as in claim 15. But Keene does not teach human or human embryonic dopamine neurons as recited in instant claims 1, 8 and 68, and does not teach autologous, heterologous or xenologous cells or tissue as recited in instant claims 16-17.

US Patent No. 6497872 (the '872 patent) teaches treatment of different neurological disorders of the CNS including with different neural stem cells including embryonic and adult human neural stem cells (see col. 13, lines 18-50, in particular). The '872 patent teaches that neuronal loss and neuronal degeneration found in several neurodegenerative diseases including Huntington disease and Parkinson's disease, which have degeneration of dopamine neurons in striatum, substantia nigra and adjacent regions of the mesencephalon (see col. 3-4; col. 27, lines 56-col. 28, line 12, in particular). The '872 patent teaches a method of treating Parkinson's disease by transplantation of human neural stem cells (see col. 13, lines 18-50; col. 42-44,

examples 14-17; col. 53-54, examples 34-36; col. 61-66, example 45, in particular). The '872 patent also teaches a method of culturing embryonic and adult neural stem cells from the brain and striata including mouse, rat and human as in claims 1, 8 and 68 (see col. 34-36, examples 1-6; col. 39-41, examples 9-12; col. 53-54, examples 34-36, in particular). The '872 patent teaches multipotent stem cells, embryonic stem cells, and adult stem cells from autologous, heterologous and xenologous cells and tissue for transplantation as recited in instant claims 16-17 (see col. 12-14; col. 13, lines 19-65, in particular).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to promote viability of human dopamine neuronal or precursor cells or human pluripotent, embryonic or adult stem cells derived from autologous, heterologous and xenologous cells and tissue for transplantation by contacting the cells with TUDCA prior to transplantation. The person of ordinary skill in the art would have been motivated to do so with an expectation of success because TUDCA has been successfully used to promote cell viability in cultured rat dopaminergic neurons or precursor cells that contain pluripotent, embryonic stem cells and embryonic ventral mesencephalic cells as taught by Keene and human stem cells derived from autologous, heterologous and xenologous cells and tissue have been used successfully used for transplantation to treat Parkinson's disease or other neurodegenerative diseases as taught by the '872 patent.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International Co. V. Teleflex Inc. 82

USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, the claimed invention is to simply substitute the human dopamine neurons or precursor/stem cells for transplantation as known in the method of the '872 patent with the rat dopamine neurons or precursor/stem cells using the method of Keene to obtain predictable results to promote viability of a transplant cell population. Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR

International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Conclusion

8. NO CLAIM IS ALLOWED.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
March 24, 2010

/Christine J Saoud/
Primary Examiner, Art Unit 1647